# EXHIBIT B

**Expert Report of Rebecca M. Ryder, M.D.**

**MDL General Report – PROLIFT**

I have prepared this Expert Report in the matter of In re: Ethicon, Inc. Pelvic Repair System Products Liability Litigation, MDL No. 2327, currently pending in the United States District Court for the Southern District of West Virginia, before the Hon. Joseph R. Goodwin. My opinions set forth in this report are made to a reasonable degree of medical certainty, and are based on information and knowledge I have acquired from my education, training, personal experience in private practice, teaching, discussion and interaction with other pelvic surgeons in professional activities and conferences, research and review of medical literature and records.

## I. Background and Education

I am a Board-Certified OB/GYN and received my subspecialty certification in Female Pelvic Medicine and Reconstructive Surgery in June 2013, which was the first time the subspecialty certification was offered. I did my undergraduate and graduate medical education at the University of North Carolina at Chapel Hill, where I also did my residency in Obstetrics and Gynecology, finishing in 1993. After completing residency with distinction as Chief Administrative Resident, I joined the faculty at Duke University Medical Center with a joint appointment in OB/GYN and Family Medicine. I began my subspecialization in Urogynecology, training with Dr. Rick Bump, Dr. Alan Addison and Dr. Christie Timmons, being in clinic with them, seeing patients for evaluation and scrubbing in surgery with them.

I moved to Norfolk, Virginia in 1994 as Assistant Professor at Eastern Virginia Medical School in the Department of Obstetrics and Gynecology. I continued training in Urogynecology

with Dr. Ralph Chesson, OB/GYN, and Dr. Steve Schlossberg, Urology, who were the Urogynecology professors and faculty members at the time. After training with them, I became the Division Director for Urogynecology at Eastern Virginia Medical School, a position I held until I left the school three years later. I served an additional year as Director of Urogynecology when the school needed faculty in that Division from 2004-2005.

I have been in private practice in Chesapeake, Virginia, since 1998. I treat women for many gynecologic and urogynecologic conditions including uterine prolapse, cystocele ("dropped bladder"), vaginal prolapse, rectocele, enterocele (vaginal hernia) and vaginal prolapse after hysterectomy, as well as stress and urge urinary incontinence and fecal incontinence. Since my residency, I have performed over 1000 surgeries for repair of pelvic organ prolapse and/or incontinence. The prolapse repair surgeries have included: vaginal, abdominal and laparoscopic hysterectomy, uterosacral ligament suspension, native tissue repairs for cystoceles, rectoceles and enteroceles, paravaginal defect repairs both abdominally and vaginally, biologic graft reinforced repairs, abdominal sacral colpopexy, and vaginal mesh procedures. I have also performed anti-incontinence surgeries including retropubic urethropexy, autologous fascia lata and biologic graft sling, needle urethropexy, tension-free vaginal tape (TVT), transobturator tape (TOT) and single incision sling. I have performed approximately 100 Prolift procedures and continue to use vaginal mesh in appropriate patients. My Curriculum Vitae is attached as Exhibit A.

## II. Materials Reviewed

In preparing this report, I have reviewed the pertinent medical literature surrounding pelvic organ prolapse, surgical and nonsurgical treatments, including published studies and abstracts

presented at national and international society meetings, FDA Public Health Notifications, Position Statements from the American Urogynecologic Society, the American Urological Association, the Ethicon Prolift Instructions for Use, Patient Brochures, Professional Education Slides, Surgeon's Resource Monograph, Surgical Technique Guide, Pelvic Organ Prolapse Counseling Guide, Gynemesh PS Instructions for Use and other materials. I have also reviewed expert reports submitted by plaintiffs' designated experts. A list of materials which I have reviewed in considering my opinions and preparing this report is attached as Exhibit B.

## III. Pelvic Organ Prolapse

Pelvic organ prolapse is a very common medical condition for women, and is defined as descent of one or more of the pelvic organs. The conditions are described as: cystocele ("dropped bladder"), uterine prolapse, vaginal wall prolapse, enterocele ("vaginal hernia") and rectocele ("rectal hernia"). Pelvic organ prolapse (POP) can be seen in 40 to 60% of women who have delivered a child (Handa 2004, Hendrix 2002), and can also occur in women who have not had a baby. There can be anatomic, functional, and psychological impacts of POP. The condition may carry minimal symptoms in early (stage I) prolapse, or as the organs descend, many women will note pelvic heaviness, a vaginal protrusion, bulge or lump, backache, and difficulty emptying their bladder or bowels. This can lead to increased frequency of urination, urinary tract infections or constipation.

Prolapse can affect a woman's ability to perform physical tasks around the home or at work, and may restrict their ability to exercise or the types of exercise they do. Varying degrees of interference with sexual function can be seen, including avoidance of sexual activity, pain with intercourse (dyspareunia), and loss of urine with intercourse (coital incontinence). Women

may feel embarrassment, shame or fear regarding their condition. They may be concerned they will be less attractive to their partner, or their partner may be afraid to engage in normal sexual activities due to the prolapse.

Many women with POP also report stress urinary incontinence (SUI) - leaking of urine with coughing, sneezing or straining, or urge urinary incontinence (UUI) – the loss of urine preceded by a sudden, strong urge to urinate. Approximately 55% of women with stage II or greater prolapse will have some stress urinary incontinence (Maher 2013). A woman carries a lifetime risk of surgery for POP or stress urinary incontinence of up to 20%. (Wu 2014.)

Pelvic organ prolapse is diagnosed on an office pelvic examination, and is graded in severity from Stage I (least) to Stage 4 (most severe). Stage I prolapse is usually minimally symptomatic, when the descending organ is only about halfway down the vaginal canal. Stage II POP involves descent of the organ to or just past the vaginal opening. As the descent continues, it can increase to a Stage 4 prolapse, when the vagina is basically turned inside out and can protrude 4 inches or more outside the vaginal opening.

The Baden Walker "halfway" system of quantifying pelvic organ prolapse was commonly used for many years, and is still in use in some literature today. It defines Stage 1 prolapse as halfway down the vaginal canal, stage 2 prolapse to the hymen, Stage 3 halfway beyond the hymen, and Stage 4 as complete vaginal eversion.

In 2002, the International Continence Society adopted the Pelvic Organ Prolapse Quantification system (POP-Q) as a standardized, reproducible system for reporting stages of prolapse, and it was widely adopted by the American Urogynecologic Society, the Society of Gynecologic Surgeons and the American Urological Association. During a POP-Q examination, up to 9 points

are measured in centimeters: 2 points on the anterior vaginal wall, 2 on the posterior vaginal wall, 2 at the vaginal apex and/or cervix, and measurements of the genital hiatus (vaginal opening), perineal body and total vaginal length. Stage 1 prolapse of any compartment descends to higher than 1 cm above the hymen. Stage 2 prolapse descends from 1cm above the hymen to 1 cm past the hymen (-1 to +1). This stage is particularly problematic in that many patients will not be symptomatic at the -1cm mark, but will become symptomatic at the 0cm or +1 cm mark. So some patients with stage 2 POP will be symptomatic and some will not. Stage 3 prolapse describes descent greater than 1 cm past the hymen, and Stage 4 prolapse descends from the total vaginal length (TVL) - 2cm to the TVL.

A condition that often occurs in peri- or postmenopausal women is vaginal atrophy. In this condition the vaginal walls have thinned due to the loss of estrogen throughout the body. It can lead to vaginal pain, avoidance of intercourse, pain with intercourse, and can also potentially increase urinary incontinence. Atrophy may increase the risk of a vaginal mesh exposure after pelvic reconstructive surgery with grafts.

## IV. Treatment of Prolapse

Prolapse does not have to be treated if the woman is not bothered by it. However, if the patient has significant prolapse symptoms, she can be offered nonsurgical or surgical treatment.

Nonsurgical treatment of POP includes pelvic floor muscle training (PFMT), either done by the patient herself at home or with the help of a specially trained physical therapist, or the insertion of a pessary. Physical therapy can be effective in reducing or alleviating prolapse symptoms, particularly in stage I or 2 prolapse. Stage 3 and 4 prolapse are almost never treated satisfactorily with PFMT alone. Although PFMT has been utilized successfully by many patients for

years, the quality of studies regarding its effectiveness is poor. In a recent Cochrane Database Review by Hagen published in 2011, only 6 studies met the inclusion criteria, some with small numbers of patients. However, they did find a 17% increased chance of an improvement in prolapse stage by compared to no PFMT. The two trials which measured pelvic floor muscle function found better function (or improvement in function) in the PFMT group compared to the control group.

Pessaries are silicone devices of various sizes and shapes that are inserted into the vagina in the office. They have to be removed and cleaned periodically, and many need to be removed for intercourse. Pessaries can be successfully fit in 41-74% of women, but need continued maintenance. Success rates of up to 62% have been reported, with up to 53% of women continuing pessary use 3 years after successful pessary fitting. (Jones 2010.) Side effects of pessary use range from vaginal bleeding, discharge and odor to, rarely, vesicovaginal or rectovaginal fistulae and pessary impaction. Pessaries are not a permanent solution, however, and the prolapse immediately recurs once the pessary is removed. Many women choose not to use a pessary due to the recurring nature of the maintenance required either by the patient herself, or by requiring physician's office visits every few weeks to months for pessary removal and cleaning.

Surgical therapies for pelvic organ prolapse include hysterectomy or hysteropexy, anterior and posterior vaginal repairs (colporrhaphies), vaginal or abdominal repairs of enteroceles or vaginal vault prolapse, and colpocleisis. Some example of vaginal vault suspension procedures are sacrospinous ligament fixation, uterosacral ligament suspension, and abdominal sacral colpopexy. Abdominal and vaginal paravaginal repairs can also be used to treat cystoceles. Anterior and posterior vaginal repairs, vaginal vault suspensions, and uterine suspensions without hysterectomy can be done with the patient's own tissue and sutures (native tissue repairs), or with

biologic or synthetic grafts. Biologic grafts can come from pigs (porcine), cows (bovine) or human organ donor grafts (dermal or fascial grafts). Synthetic grafts have been utilized in pelvic reconstructive surgery and reported upon since 1962, and can be permanent or absorbable.

Hysterectomy involves the removal of the uterus and usually the cervix, and is most commonly done vaginally in the case of uterine prolapse. It is often combined with a suspension stitch or stitches afterwards, to suture the vagina to ligaments in the pelvis to help prevent it from falling back down later (recurrent prolapse). Uterine suspension procedures can be done abdominally or laparoscopically to the patient's own ligaments, to help relieve the prolapse and retain the uterus, but these have a very high recurrence rate. Some surgeons perform uterine suspension procedure with synthetic mesh, either to the sacrospinous ligaments vaginally, or the anterior longitudinal ligament of the sacrum via an abdominal incision, laparoscopically or robotically (hysteropexy).

Anterior and posterior vaginal repair (colporrhaphy) and perineoplasty are native tissue prolapse repairs. In this procedure, an incision is made on the skin between the vagina and bladder in the anterior wall and/or in the skin between vagina and rectum in the posterior vaginal wall. Breaks in the connective tissue between the vagina and the prolapsing organ are repaired and reinforced with sutures between the vagina and bladder or rectum to prevent organ descent and bulging into the vaginal canal. During a perineoplasty additional sutures are placed at the opening to the vagina to close any gaping of the vaginal opening and reinforce pelvic support to help reduce recurrence of a pelvic support defect. The perineoplasty is similar to repairing an episiotomy after childbirth; it is sometimes performed on women with complaints of vaginal laxity.

Enteroceles are basically vaginal hernias, where there is a break in the connective tissue deep in the pelvis that allows intestinal contents to herniate, or drop down, behind the vagina and push the vagina out. They can be repaired vaginally with sutures, by opening the vaginal wall, finding the sac of the hernia, closing off the sac with sutures and suspending and suturing the vaginal wall. They can also be repaired in a similar fashion laparoscopically or robotically.

The top of the vagina after a hysterectomy has been performed is called the vaginal apex, and it can detach from its support ligaments and cause a bulge or protrusion called a vaginal vault prolapse. This can occur with or without an enterocele. Vaginal vault prolapse is repaired with a sacrospinous ligament fixation (SSLF), uterosacral ligament fixation (USLS), or abdominal sacral colpopexy (ASC). In the SSLF, the upper vagina is sutured to a ligament deep in the pelvis, usually on the patient's right side, that goes from the sacrum to a pelvic bone - the sacrospinous ligament. In the USLS, the vagina is sutured to 2 ligaments that go from the sacrum to the vagina called the uterosacral ligaments. In the ASC, the vagina is sutured via a synthetic graft to a ligament along the anterior surface of the sacrum. The vagina is not long enough to reach the sacrum, so an "extension graft" must be used to add the length to reach the sacrum.

Abdominal and vaginal paravaginal repairs are done to repair breaks in the continuity of the connective tissue under the bladder, in which the tissue has detached from the sides of the pelvis, allowing the bladder to drop down. In these repairs, the connective tissue beside the bladder is reattached to ligaments overlying the muscles deep on the sides of the pelvis, the arcus tendineus.

Colpocleisis is an obliterative vaginal surgery that reduces the prolapsed organs, removes vaginal epithelium and basically sews the vagina shut. It is most often used in elderly patients

who are not good surgical candidates for lengthier pelvic reconstructive surgeries, and who do not wish to retain sexual function.

Complications of any form of surgical treatment of POP may include injury to the bladder, ureters, small intestine or rectum, urinary tract or wound infections, excessive bleeding intra- or post-operatively, recurrent prolapse, anesthetic complications, and, rarely, death. New onset urinary incontinence may occur either from changing vaginal angles resulting in new SUI, or bladder irritation or other unknown factors leading to UUI.

Postoperative dyspareunia or pelvic pain are also well-known potential surgical risks. Weber et al. reported a 19% dyspareunia rate following surgery for prolapse or incontinence in native tissue repairs. (Weber 2000.) A survey aiming to assess sexual function after native tissue prolapse surgery found that for 25% of participants, vaginal pain was the single most bothersome barrier to intercourse. (Pauls 2007.) Dyspareunia has most often been associated with posterior colporrhaphy, with or without levator plication (Kahn 1997), but has been reported after all POP surgeries, in rates ranging from 0 to 57% (Dietz 2013). Two large reviews of sexual function after POP surgery have concluded no difference in de novo dyspareunia between native tissue and synthetic graft repair. (Dietz 2013, Maher 2016.) The most recent Cochrane Review meta-analysis of randomized controlled trials (RCTs) concluded there was no difference in de novo dyspareunia rates between native tissue repair (9.5%) and synthetic mesh repairs (8.8%). (Maher 2016.)

Risks of surgeries utilizing synthetic grafts include mesh exposure or erosion into nearby structures, infection, scarring, and possible shrinkage of the mesh and/or scarring or contraction of the surrounding vaginal tissues. This risk is discussed in the physician's training for Prolift as well as the Instructions for Use which warns of "scarring that results in implant contraction." It

should be noted that permanent surgical sutures used in native tissue repairs and ASC can also erode into nearby organs or the vagina. Abdominal prolapse surgeries like ASC also have risk of mesh exposure or erosion as well as risks of hemorrhage, adhesion formation and possible later small bowel obstruction.

The first published report analyzing polypropylene mesh tissue reaction and possible degradation was published in 2001, looking at Mersilene mesh slings vs. Prolene TVT. (Falconer 2001.) Their conclusions from vaginal biopsies reported a "minimal inflammatory reaction without a significant change in collagen" in the Prolene TVT group versus a "significant foreign body reaction" in the Mersilene group. In 2008, a case series of 24 explanted slings was reviewed, 10 of which were polypropylene mesh. In these tissue samples explanted at 2-34 months after implantation, the polypropylene grafts had the best host tissue integration and "no demonstrable graft degradation." (Woodruff 2008).

The American Urogynecologic Society (AUGS) and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), the leading societies for pelvic reconstructive surgeons, jointly issued a "Frequently Asked Questions by Providers" paper on MidUrethral Slings for Stress Urinary Incontinence in March of 2014. They also conclude that there is no peer-reviewed literature suggesting clinically significant degradation of polypropylene mesh, and cite the 17 year followup study of TVT (Nilsson 2013) showing "excellent durability and safety of the procedure." The Prolift mesh is made of the same material as PROLENE permanent surgical suture, which has been used for over 50 years. I have seen no fraying or degradation of polypropylene mesh in my patients. Polypropylene mesh is also the most widely used graft for the ASC, so any change in structure, host reaction or degradation that could occur would also apply to the use of mesh in any pelvic reconstructive surgery.

## V. Prolift Pelvic Floor Repair System

For years, gynecologists have struggled with significant prolapse recurrence rates after hysterectomy or POP repairs, ranging from 20-37%. (Berrocal 2004.) The factors contributing to this may include using the patients' own weakened or torn tissue in native tissue repairs, underlying connective tissues disorders, and chronic gravitational forces on the pelvis with normal activities of daily living that increase pelvic pressure, like coughing, straining, defecation and high-impact exercise or heavy lifting. This has led gynecologists to look for other alternatives beyond native tissue repairs to increase durability of surgical procedures and decrease recurrence rates.

The first use of a synthetic graft for the repair of post-hysterectomy vaginal vault prolapse was described by Lane in 1962. He describes what is now known as an abdominal sacral colpopexy using "synthetic used for arterial grafting." (Lane 1962.) Since that time, multiple synthetic grafts have been used and reported upon for POP repair, including Teflon, Dacron, Goretex, Mersilene and polypropylene permanent synthetic grafts, as well as Dexon and Vicryl absorbable meshes. Advantages of using a prepared synthetic mesh include decreased operative time and morbidity for the patient in not having to harvest her own tissue for use in the repair, and reproducibility in the properties of synthetic mesh over potentially poorer quality tissue for repair from the patient who has already experienced a failure of her native tissue.

Initially, the literature focused primarily on synthetic mesh use for abdominal sacral colpopexy (ASC), with one report of Marlex mesh for rectocele repair. (Parker 1993.) In her 1997 review of synthetic graft use in gynecologic surgery, Iglesia cites a 9-11% mesh erosion rate for ASC with these older synthetic meshes. (Iglesia 1997.) Potential complications of graft use in-

clude wound infection, rejection, need for mesh removal, sinus tract formation and graft erosion through the vaginal apex.

Pelvic reconstructive surgeons were inspired by the general surgery literature that showed a reduction in abdominal hernia recurrence by augmenting their native tissue repair with synthetic mesh grafts, most commonly polypropylene. Polypropylene mesh use in the vagina was first reported in 1994 by Ulmsten and Petros, using that mesh for the very successful tension free vaginal tape, Gynecare TVT Tension Free Support for Incontinence. This inspired surgeons to consider using polypropylene mesh vaginally for repair of POP, primarily for those patients with cystoceles and rectoceles, to avoid abdominal surgery with its attendant risks. Initial studies report surgeons fashioning freeform trapezoidal or hammock-shaped polypropylene mesh overlays to reinforce colporrhaphies, as described by Nicita in 1998 and Miglairi in 1999 and 2000. The grafts were secured to the arcus tendineus, pubocervical fascia and/or cardinal/uterosacral ligament complexes with sutures. Initial results were promising with follow-up to 23 months, with no significant complications or mesh exposures.

In 2000, a group of 9 gynecologists convened in France to report and analyze their work in using synthetic tension free vaginal meshes (TVM) for pelvic organ prolapse repair. Their goal was to perfect a less invasive, tension-free repair to produce durable repairs which reduced postoperative pain, reduced difficulty in passage of bowel movements and prevented narrowing of the vagina and dyspareunia that could be seen after traditional native tissue repairs. Many types of meshes were discussed and existing literature reviewed. Ultimately, this group decided that lightweight, macro porous polypropylene mesh – Gynecare Gynemesh PS -- had the most advantages over other existing materials. Gynemesh PS employed the same PROLENE polypropylene utilized in TVT but in a different knit construction. They underwent a feasibility as-

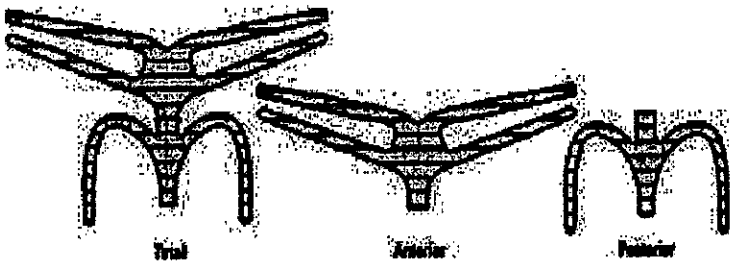
sessment including cadaver studies and approximately 300 surgical interventions, and standardized the TVM procedure and protocol. A scientific, prospective study was initiated with an expected duration of 5 years. Gynemesh PS was FDA approved in the United States for pelvic organ prolapse repair in 2002.

Encouraged by positive results in the studies of Migliari and Nicita, and the experience of the French TVM group, physicians from the United States began training with the TVM group in France in 2004. A published abstract from the International Continence Society meeting in 2005 reported on Prolift TVM in 687 patients, with a 94.7% cure rate and a 6.7% incidence of granuloma formation or vaginal erosion. (Cosson 2005.) Ethicon made the Prolift vaginal repair kit available in the US in 2005.

I personally received my training in the Prolift procedure in 2007, and began using it in my patients shortly thereafter. I have performed approximately 100 Prolift cases, and continue to use vaginal mesh to augment repairs in some patients. Before the Prolift system was available, I performed approximately 50 grafted repairs using biologic materials and 30 or so using freeform grafts that I cut myself out of Gynemesh PS or other polypropylene material. I decided to investigate further and ultimately use the Prolift system in my patients due to the positive experience of leaders in the field, the consistency of the product and the reproducibility of a standardized POP repair procedure. I also saw value in providing a tension-free repair not relying solely on sutures for maintenance of pelvic organ support.

The Prolift system includes an anterior, apical and posterior Gynemesh PS graft altogether in the Total Pelvic Floor Repair System, or may have just an anterior graft (Anterior Pelvic Floor Repair System) or posterior graft (Posterior Pelvic Floor System). Also included is a

Guide, cannulas and retrieval devices that help deliver the graft to the appropriate places in the pelvis.



For the anterior portion of the procedure (correcting a cystocele), an incision is made on the anterior vaginal wall and two incisions are made on each side of the patient's inner thigh just beside the pelvic bone. The graft has 4 arms, and the guide with a cannula over it is inserted from the outside of the thigh in to the vaginal incision. The guide is removed and a retrieval device is passed down the cannula from outside in, and the arms of the graft are pulled through the cannula. The arms are pulled just enough to have the central portion of the mesh lay flat under the bladder, leaving a tension free support for the bladder. The mesh is trimmed as appropriate to fit the patient's anatomy. The lower portion of the mesh is secured with a suture to the vaginal apex to support it as well. The vaginal incision is closed, the anterior vaginal wall is supported by the surgeons hand to avoid any overtightening, and the cannulas are removed. Excess mesh arms are trimmed at the skin and skin incisions closed. Posteriorly, a second vaginal incision is made and two small incisions are made in the patient's buttocks. The guide is placed from the buttock up through the sacrospinous ligament on each side, and 2 arms are pulled posteriorly through the ligament. The mesh is made to lay flat under no tension across the top of the rectum, the mesh is trimmed to fit the patient's anatomy, the top of the mesh is secured to the vaginal apex, and the

bottom of the mesh secured to the lower part of the vagina. The vagina is closed, cannulas are removed and excess mesh arms trimmed at the exit point.

## VI. Prolift Instructions for Use, Professional Education and Patient Materials

I have reviewed the Prolift Instructions for Use, Surgeons Resource Monograph, Surgical Technique Guide, Ethicon Professional Education Slides used for physician training, and patient brochures for Prolift. I find the resources to be informative and more than adequate in discussing patient selection, technique, and risks of the procedure and their management. The Instructions for Use clearly state the indications, contraindications, warnings, precautions and adverse reactions with use of the mesh. It also describes the clinical performance of the Prolift system in ongoing observational studies from France and the U.S.

The Surgeon's Resource Monograph also devotes 4 pages to discussing possible complications noted above (hemorrhage, visceral injury, infection, mesh complications, vaginal pain and dyspareunia) and their management.

The Professional Education Slides appropriately present the history of the Prolift device and the relevant studies. They clearly list rates of potential complications as well, including mesh exposure and dyspareunia. Of course a pelvic reconstructive surgeon would already be well aware of the risks of pelvic surgery, including but not limited to damage to surrounding organs, vessel or nerve injury, infection, and risk of postoperative pelvic pain or dyspareunia. Those risks are common to all POP surgeries and are therefore within the common knowledge of pelvic floor surgeons. Vaginal mesh exposure is also seen and has been reported on for years in the medical literature with the ASC. The professional education slides for Prolift addressed numer-

ous potential complications, including mesh exposure, as well as options for treating complications.

The patient brochures are also clear and informative regarding what POP is, what treatment options are including non-surgical treatments like physical therapy or pessaries, what Prolift is, and its accordant risks. The Prolift patient brochure in 2005 discusses risks including "injury to blood vessels of the pelvis, nerve damage, difficulty urinating, bladder and bowel injury. There is also a small risk of the mesh material becoming exposed into the vaginal canal." It also lists all the risks that are discussed in the warnings and adverse events sections of the IFU. The Prolift brochure was revised in 2008 to include additional detail. Ultimately, the Prolift patient brochures appropriately fulfill the limited purpose of a patient brochure and are not false or misleading.

The patient brochure, while helpful as a tool for surgeons to use, is no substitute for a comprehensive informed consent discussion between surgeon and patient. I did utilize the Prolift brochures as a "take-home" for the patient in addition to extensive verbal counseling during the office visit. It is the responsibility of the surgeon – not a brochure – to explain fully to the patient the potential risks of the device and the surgery. All pelvic reconstructive surgeons should advise their patient of the risk of vaginal or pelvic pain or dyspareunia after any pelvic reconstructive surgery. It is also the surgeon's job to make the patient aware that a mesh exposure may require medication or further surgical treatment. Physicians are trained in informed consent, surgical technique, complications and their management in their residency (and some in a fellowship), and had further very adequate training of any unique risks in using the Prolift system by the Ethicon training materials and hands-on training.

## VII. Medical Literature

To date there are over 200 published reports in the medical literature on Prolift, more than any other vaginal mesh application or kit. My search of the medical literature found published Prolift studies beginning in 2007. (Fatton 2007.) In this retrospective study of 110 patients with stage 3 or 4 prolapse, failure rate (even low grade or asymptomatic) was 4.7%, with a 4.7% mesh exposure rate at 3 months. By 2008, eight published Prolift studies of 1298 women were included in a review by Feiner. With an average of 30 weeks follow-up, these studies averaged an 86.8% success rate, with a 5.7% mesh erosion rate and a 2.1% dyspareunia rate.

The experience of 3 U.S. centers participating in the initial prospective TVM studies was reported in 2011. (Miller 2011.) In this trial of 85 patients, the 5 year success rate, defined as leading edge above the hymen, was found to be 89%. Mesh exposure rate was 19%, but 21% of their patients had a concomitant hysterectomy, which is known to increase the chance of a mesh exposure. Their population had a 30% pre-surgery dyspareunia rate (12 of 40 sexually active patients). In 8 of those 12 patients, dyspareunia resolved after TVM surgery. There were 3 cases of de novo dyspareunia (3.5%).

The five year follow up on the initial TVM study group from France was published in 2013, and showed a composite 84% success rate at 5 years, defined as the leading vaginal edge above the hymen, the patient having no bulge symptoms, and no surgical re-intervention for recurrent prolapse (Jacquetin 2013.) New onset dyspareunia was reported in 10% of patients, and one patient reported new onset pelvic pain at 5 years.

Prospective randomized controlled trials (RCTs) are considered the highest level of evidence in clinical studies, in that they study all patients assigned to a particular intervention and get real time (prospective) data as it occurs, comparing different treatments, rather than relying

on data recall or chart reviews. As of this report, there are 8 RCTs to date on Prolift, depicted in Table 1 (see attachment). The studies total 1215 patients, comparing Prolift to native tissue repairs such as anterior and/or posterior colporrhaphy, or SSLF. Seven of the studies noted lower recurrent prolapse rates with Prolift, and the one remaining study of 65 patients (Sokol 2012) noted equivalent recurrent prolapse rates in both groups. Patient quality of life improved in all studies in which it was measured, with the Prolift groups demonstrating either equivalent or superior improvements. Mesh exposure rates ranged from 3.2 to 20.8%. Six of the studies reported on dyspareunia. Four of the 6 studies found higher postoperative dyspareunia rates in the native tissue repair group. The remaining 2 studies found no difference between native tissue and Prolift groups in postoperative dyspareunia. These best-quality research studies are nearly universally consistent in their findings of better postoperative results, less recurrent prolapse, and no increased dyspareunia with use of the Prolift system. These RCTs suggest Prolift to be the more durable operation with better results for the majority of patients.

The first Cochrane Review of POP surgery also provides important information on the use of mesh to treat prolapse. The Cochrane Collaboration is an international, volunteer, not-for-profit research group formed to organize medical research information to facilitate the choices that health professionals, patients, policy makers and others face in health interventions, according to the principles of evidence-based medicine. The group conducts systematic reviews of randomized controlled trials of health-care interventions, which it publishes in The Cochrane Library. The Cochrane Collaboration published a review entitled "Surgical management of pelvic organ prolapse in women" in 2013 (Maher 2013), which would be considered a gold-standard resource for physicians and patients in the treatment of POP. The Authors' Conclusions of that review, looking at 56 RCTs of all types of meshes, kits and procedures, state: "The use of mesh

or graft inlays at the time of anterior vaginal wall repair reduces the risk of recurrent anterior wall prolapse on examination. Anterior vaginal polypropylene mesh also reduces awareness of prolapse, however these benefits must be weighted against increased operative time, blood loss, rate of apical or posterior compartment prolapse, de novo stress urinary incontinence, and re-operation rate for mesh exposures associated with the use of polypropylene mesh." They also note "no differences in quality of life data or de novo dyspareunia were identified." Mesh erosions were reported in 11.4%, with surgical intervention in 6.8%.

This year the Cochrane Collaboration published another review of POP surgery focusing on mesh and grafted repairs entitled "Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse" (Maher 2016). Their conclusions, analyzing 37 RCTs of 4023 women, are as follows:

1. Patient awareness of prolapse and recurrent prolapse on examination were less likely after mesh repair.
2. Rates of repeat surgery for prolapse were lower in the mesh group.
3. Eight percent of women in the mesh group required repeat surgery for mesh exposure.
4. There was no difference in de novo dyspareunia between the groups.
5. Although de novo stress incontinence was higher in the mesh repair group, there was no difference between groups in repeat surgery for continence.

The Society of Gynecologic Surgeons' Systematic Review Group published a meta-analysis of "Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials" in 2011. (Abed 2011.) Their conclusions note an overall graft erosion rate of 10.3%, which is comparable to graft erosion rates from ab-

dominal sacral colpopexy. The dyspareunia rate was 9.1%, not significantly greater than dyspareunia rates published for native tissue repairs, as confirmed by the Dietz 2013 and Maher 2016 studies noted above.

I do not see reliable support in the medical literature for the argument by the plaintiffs' experts of a chronic and severe inflammatory response to polypropylene mesh. The Prolift IFU informs surgeons that Gynemesh PS "elicits a minimum to slight inflammatory reaction, which is followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, thus incorporating the mesh into adjacent tissue." While there may be a response on a histological level, I have not seen a body of evidence demonstrating a chronic and severe inflammatory response. Nor have I personally seen chronic and severe inflammatory responses in my patients, or those who have been referred to me, with polypropylene mesh grafts.

## VIII. Summary

The high failure and/or recurrence rate of POP surgery has led innovators in the field of pelvic reconstructive surgery to search for better ways to perform these very common operations. Thorough, meticulous and deliberate study has been undertaken to find the most efficacious means possible to achieve the best possible outcomes for our patients. Experts in the field devised the TVM procedure, from which Prolift ultimately evolved. Multiple studies and my own clinical experience show that grafted repairs have better initial results and more durable surgical outcomes than our traditional native tissue repairs. The risk of vaginal mesh erosion should be discussed with patients preoperatively, but is not significantly greater on average than the risk of vaginal mesh erosion with abdominal sacral colpopexy, which has been performed since 1962. Postoperative dyspareunia can occur in both grafted and native tissue POP repairs, and also

needs to be discussed with the patient preoperatively. I personally have seen no serious complications with use of the Prolift procedure and continue to offer graft repairs to my patients when indicated.

## IX. Opinions

The following are my opinions on Prolift, which I hold to a reasonable degree of medical certainty. I reserve the right to amend my opinions as I review additional information.

1. Gynecare Prolift is a safe and effective product that is supported by a substantial amount of clinical data, particularly when compared to alternative surgical approaches to treat prolapse. It is an appropriate treatment option for many women who suffer with this difficult and embarrassing condition. From my perspective as an experienced pelvic floor surgeon, and based on my review of the medical literature on Prolift and the use of transvaginal meshes to treat prolapse, Prolift's benefits far exceed its risks for many women and it is not defectively designed.

2. The Gynecare Gynemesh PS mesh used in Prolift is an appropriate, effective and safe material for use in this indication. Polypropylene mesh and sutures have been used an implant for decades. The pore size is sufficiently large to allow for proper tissue ingrowth, and has not presented increased risks of infection, particularly in relation to other implants.

3. The body of clinical data for Prolift (and TVT, for that matter) does not support the conclusion that PROLENE® Soft mesh degrades in the body in any manner that has a clinical impact on patients. If it did degrade in a clinically significant way, surgeons would see far lower levels of durability in their Prolift repairs, and that is certainly not something that I have seen in my clinical practice over many years. Nor would it make sense given that PROLENE®

sutures have continued to be used in countless surgical applications for decades, including cardiac surgery.

4. The possible risks of Prolift are adequately described in the Prolift IFUs, the Surgeon's Resource Monograph and professional education slide decks. The IFU and the professional education materials appropriately take into account the foundational level of knowledge of the implanting surgeon.

Dated: February 27, 2016

Rebecca M. Ryder, M.D.

**Table to Ryder General Report on Prolift**

| Author and date | # subjects | Intervention | Significant findings | Mesh exposure | De novo dyspareunia |
|---|---|---|---|---|---|
| Nguyen 2008 | 76 | anterior colporrhaphy (AC) vs. Prolift anterior | "optimal and satisfactory anterior vag support" in 55% of AC group vs. 89% of Prolift group | 5% | 16% in AC group vs. 9% in Prolift group |
| Iglesia 2010 | 65 | native tissue repair + vag hyst vs. Prolift anterior or total | 59.4% recurrence mesh vs. 72.8% no mesh (p=.28); point Ba signif. higher in mesh group | 15.6% | "insufficient data" |
| Altman 2011 | 389 | anterior colporrhapy (AC) vs. Prolift anterior | 60.8% success in Prolift vs. 34.5% in AC; signif less sxs of vag bulge in Prolift group and signif higher rate of stage 0 or 1 prolapse | 3.2% | not reported (NR) but no difference btw groups in PISQ scores |
| Withagen 2011 | 200 | conventional native tisse repair as indicated vs. Prolift ant, post, or total | 9.6% prolapse recurrence at 12 months in the Prolift group vs. 45.2% in conventional group. In both groups, dyspareunia decreased at 12 months with no sig difference btw groups | 16.9% | 8% in Prolift group, 10% in conventional group |
| Halaska 2012 | 168 | sacrospinous fixation (SSF) vs. Prolift total | at 12 months, prolapse recurrence in 16.9% of mesh group and 39.4% of SSF group; no difference in QOL improvement, de novo SUI or OAB | 20.8% | 8.0%(no significant difference from SSF group) |
| Sokol 2012 | 65 | conventional native tissue repair vs. Prolift ant, post, or total | no significant differences between groups in recurrent prolapse; signif improvement in QOL in both groups; improved PISQ scores in both groups with no diff btw groups | 15.6% | 9.1% mesh group, 21.4% no mesh group |

| | | | | | |
|---|---|---|---|---|---|
| Svabik 2014 | 70 | SSF vs. Prolift total | 97% success rate Prolift vs. 65% SSF | | 5.6% postop dyspareunia; no difference PISQ scores, NR if dysparuenia was preexisting or de novo |
| daSilveira 2014 | 184 | conventional native tissue repair vs. Prolift | cure rates in anterior compartment signif. better in mesh group; QOL scores better in mesh group | 20.0% | 6.2% native tissue vs. 3.4% mesh (NR whether de novo) |